

APPLICANT(S): SIEGEL, Steven  
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## **REMARKS**

The present response is intended to be fully responsive to all points of rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

### **Status of Claims**

Claims 1-45 are pending in the application. Claims 1-20 have been rejected. Claims 21-45 were withdrawn. No claim is canceled herein. Claim 1 is amended herein. Support for this amendment can be found, at least, in Figures 3, 4, and 18.

### **EXAMINER INTERVIEW**

Applicants note that Applicants' representative Prakash Subbiah spoke with Examiner Wax and Examiner Al-Awadi over phone. Applicants thank the Examiners for their courtesy during the telephonic interview. Applicants discussed the outstanding issues to advance the prosecution. Specifically, in order to overcome the obviousness rejections, Applicants pointed out the distinctions between the claimed invention and the cited references. Examiner Wax suggested that Applicants submit a Declaration, under 37 C.F.R. § 1.132, discussing a basis for the distinctions. The Examiners noted that they would consider removing the rejections after receiving this Response.

### **CLAIM REJECTIONS**

#### **Rejections Under 35 U.S.C. § 103**

In the Office Action, the Examiner rejected claims 1-13 and 15-20, under 35 U.S.C. § 103, as allegedly being obvious over Siegel (U.S. Patent Application Publication No. 2002/0179096; "Siegel") in view of Kino *et al* (U.S. Patent No. 5,871,778; "Kino"). Specifically, the Examiner asserts that Siegel teaches a surgically implantable drug delivery device for long-term delivery of the antipsychotic drug and Kino teaches risperidone. Accordingly, the Examiner finds that it would have been obvious to combine the references to arrive at the invention. Applicants respectfully disagree for the reasons set forth below.

Applicants submit herewith a Declaration ("Declaration"), under 37 CFR § 1.132, from Dr. Steven Siegel. Dr. Siegel is the first-named inventor in the Siegel reference, which is relied upon by Examiner for the rejections discussed herein.

Applicants note that Applicants have amended independent claim 1 and the amended claim recites "a first formulation," "a second formulation," "biodegradable polymer comprises a poly(lactide/glycolide) (PLGA) copolymer at a concentration of about 40-90% (w/w)," "drug comprises risperidone, 9-OH-risperidone, or an active metabolite thereof at a concentration of about 10-60% (w/w)," and "the time to maximum concentration of said drug in said subject ranges from about 20 days to about 190 days." Nowhere does Siegel teach or suggest this combination of claimed features. Rather, Siegel relates to haloperidol loaded implant, not risperidone loaded dual formulation as claimed. In particular, Siegel discusses implants comprising 20 to 40% haloperidol (at page 3, paragraph 23 and examples at pages 4 to 5 of Siegel), and thus Siegel's is directed to haloperidol implant, not risperidone loaded dual formulation as claimed.

As stated in the Declaration, Exhibits 1-3 that fully demonstrates that different drugs have different release rates in PLGA matrices. A type of drug plays a role in setting the release rate. See Exhibit 1 (Siegel *et al.*, *European J. Pharmaceutics and Biopharmaceutics*, 2006, vol. 64, pages 287-293); See also Exhibit 2 (Frank *et al.*, *J. Control. Release*, 2005, vol. 102, pages 333-334, published online on November 14, 2004); See also Exhibit 3 (Kiertosis *et al.*, *European J. Pharmaceutics and Biopharmaceutics*, 2005, vol. 59, pages 73-83, published online on July 2, 2004). For example, Table 1 in Exhibit 1 shows no correlation between drug types and release rates in PLGA matrices. Accordingly, as stated in the Declaration, different drugs release at different rates from PLGA matrices, and thus to infer from one drug the effects in another is misleading. Therefore, one could not expect or predict the release rate of risperidone as claimed, based on Siegel's haloperidol.

In addition, as stated in the Declaration, it is well known that these are different drugs having different chemical and physical properties. Because of the existence of chemical polymorphisms, one could not expect whether the arrangement and/or conformation of molecules in the crystal lattice would change or not while combining the drug and the polymer during solvent casting or other approaches to form an implant.

Kino does not cure the defect in Siegel. Specifically, as stated in the Declaration, Kino relates to haloperidol loaded into dl-Polylactic acid or Poly(lactic-co-glycolic) acid (50:50) for making a microcapsule, which is not an implant as claimed. Although Kino describes a laundry list of active materials including risperidone, it provides no data or support for how much of each active ingredient that can be loaded in to each biodegradable polymer to achieve the release rate as claimed. Therefore, at the maximum, Kino provides a general guidance for producing only a microcapsule with no expectation of success with respect to specific amount of drug for each combination of the drug and the polymer for an implant to provide the release rate as claimed.

As stated in the Declaration, for the sake of arguments, even if a person is motivated to try risperidone, he or she could not expect or predict that risperidone at concentrations of 10% or more would be effective with the claimed PLGA polymer. With PLGA polymer, the incorporation efficiency decreases with increasing drug concentration. See Exhibit 4 (Budhian *et al.*, 2005, *J. of Microencapsulation*, vol. 22(7), pages 773-785). Studies have shown that the final drug content in PLGA polymer has an upper limit, which cannot be increased simply by increasing the initial drug concentration. See *Id.* at 778; See also Exhibit 5 (Chorny *et al.*, 2002, *J. of Controlled Release*, vol. 83, pages 401-414); See also Exhibit 6 (Baichello *et al.*, 1999, *Drug Development and Industrial Pharmacy*, vol. 25, pages 471-476). Any such increase in the initial drug concentration would result in burst release of the drug or crystallization of the drug.

For instance, as stated in the Declaration, at higher drug loading concentrations, an initial burst of drug release was observed with PLGA microparticles. See Exhibit 7 (Choi *et al.*, 2001, *Bull. Korean Chem. Soc.*, vol. 32, pages 867-872). Specifically, at 20% initial drug loading concentration, PLGA particles released 56% of encapsulated drug in 2 hours. *Id.* at 870-871. Accordingly, the high initial drug concentrations in PLGA results in quick burst release, not long term release as claimed.

Additionally, as stated in the Declaration, at the maximum, only 2% of haloperidol could be loaded into PLGA polymer system. Any increase in drug concentration beyond 2.5 mg/ml caused the drug content to decrease because the drug molecules within the polymer matrix are attracted towards the molecules in the aqueous phase and migrate to aqueous phase and nucleate as crystals. See Exhibit 8 (Budhian *et al.*, 2007, *Intl. J. of Pharmaceutics*, vol.

336, pages 367-375). As a result, the high initial drug concentrations results in crystallization of drug. *Id.* at 372.

Therefore, an attempt to incorporate as much as 10-60% risperidone into the PLA:PGA copolymer to provide the release rate of time to maximum concentration 20-190 days, as claimed, in the subject Application cannot be expected in view of the cited references or any other reference in the art.

Additionally, the cited references, either alone or in combination, in light of the above discussed Exhibits 1-8, teaches away from incorporating as much as 10-60% risperidone into the PLA:PGA copolymer to provide the release rate of time to maximum concentration 20-190 days, as claimed, because of the problems of burst release as well as crystallization of the drug discussed above.

Since the cited references, either alone or in combination, do not teach or suggest how to arrive at the claimed 10%-60% risperidone and 40%-90% of the biodegradable polymer to achieve the time to maximum concentration of 20-190 days, they do not render the claimed invention obvious.

Surprisingly and unexpectedly, the inventors of the instant application have achieved the long term release of risperidone at the loading concentrations of 10%-60%. *See* Examples 3, 4, 8, 10 and 13 of the Specification. As discussed above, it would be unreasonable to expect initial theoretical drug concentrations of 10% or more due to possible saturation and subsequent crystallization of the drug. Therefore, it was surprising that Applicants could incorporate as much as 10-60% risperidone into the PLA:PGA copolymer to provide the release rate of time to maximum concentration 20-190 days, as claimed in the subject Application. Furthermore, Examples 3, 4, 8, 10, and 13 demonstrate the long term release of risperidone at higher concentrations. In particular, Examples 3 and 8 show that the drug was "stable" in combination with the PLGA polymer in an implant formulation. Examples 3, 4, 8, 10, and 13 show various higher concentrations of the drug and its release profiles. Higher risperidone loading concentration stabilizes the system, providing the long term release. These data clearly show the new, novel, and non-obvious biodegradable implant.

Accordingly, Applicants respectfully request withdrawal of the rejection.

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In the Office Action, the Examiner rejected claims 13 and 14, under 35 U.S.C. § 103(a), as allegedly being obvious over Siegel in view of Kino and further in view of Sidman (U.S. Patent 4,352,337) ("Sidman"). In response, Applicants note that claims 13 and 14 are dependent claims that ultimately depend from and add additional features to independent claim 1. Since independent claim 1 is patentable for the reasons discussed above, dependent claims 13 and 14 are also patentable by virtue of there dependency. Accordingly, Applicants respectfully request removal of this rejection.

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**CONCLUSION**

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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